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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/987,687	11/15/2001	Matthew C. Coffey	032775-078	7186

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,687	COFFEY ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 9/23/04. The amendment has been entered. Claims 1-21 are currently pending in the application and are examined herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 3/1/04 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (WO 99/08692, previously cited). In view of Heise et al. (Cancer Gene Therapy, 11/1/99; cited in IDS filed 3/2004).

Lee teaches a method for directly delivering an oncolytic reovirus serotype 3 Daring strain virus (which is a human serotype 3 reovirus) by injection into a solid tumor to reduce growth of the tumor. Lee teaches that the method comprises administering an effective amount of virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells and wherein the virus is administered in a single dose or in multiple doses (i.e. more than one does) and the multiple doses can be administered concurrently (at the same time) or consecutively (i.e. either before or after the base administration). (See, for instance, abstract; p.3 lines 1-15; p.9, lines 17-20; p.34, lines 9-17; Examples 9 and 10; and Claim 38).

Lee also teaches a tumor treatment wherein a tumor that has an area of with a mean area of $0.31cm^2$ are treated with an injection of oncolytic virus (see page 27, last paragraph). Using the following formulas, $AREA=4\pi(r)^2$ and $VOLUME=(4/3)\ \pi(r)^3$, the volume of the tumors was calculated to be about $0.17cm^3$. Therefore, Lee teaches an injection of oncolytic virus per $0.25cm^3$ of the tumor.

As such, Lee teaches a method of injecting a reovirus into a solid tumor (e.g., see claim 27) comprising multiple doses (i.e., multiple injections) which are administered concurrently (i.e., on the same day). Lee teaches that the method can comprise the additional administration of the therapeutic virus by other routes of administration, including systemic administration of human reovirus; or topically or by spray (e.g., see page 9). It is noted that multiple administrations encompasses more than one administration.

Lee does not explicitly teach the volume of the viral composition that is injected into the tumor or the exact number of times that the viral composition is injected into the tumor, nor does Lee teach that the oncolytic virus that is administered is a modified adenovirus, such as ONYX-015.

However, Heise teaches the importance of virus distribution when using an oncolytic virus to treat a tumor. Specifically, Heise teaches,

> "These data suggested that replication-dependent tumor cell lysis and spread was occurring, but that tumor destruction might be improved by increasing i.t. (intratumoral) virus distribution. Two treatment parameters were then varied to determine whether virus distribution, and consequently efficacy, could be improved. Divided i.t. injections of virus were more efficacious than a single injection of the same total dose. Likewise, increasing the volume of the viral suspension for i.t. injection allowed better distribution within the tumor mass and increased efficacy. These results have implications for the treatment of cancer patients with viral agents.

Clearly indicating that the when treating a cancer patient with a viral agent such as an oncolytic virus, increasing the distribution of the virus in the tumor, such as by injecting the virus multiple time or injecting a larger volume of virus solution, will increase the efficacy of the treatment. Furthermore, Heise teaches that the oncolytic virus ONYX-015 (which is a modified adenoviral vector) is injected into a C33a tumor that is ~200mm^3 wherein the virus is administered in a total volume of 100ul, which is 50% of the volume of the tumor (e.g., see p.

500, second column, second paragraph under "Effects of virus suspension volume on efficacy and i.t. distribution."). It is noted that the reovirus used by Lee and the ONYX-015 virus used by Heise are both oncolytic viruses that have can be used for tumor treatment.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method taught by Lee to make a method for delivering a virus to a solid tumor by administering on the same day a composition comprising either an oncolytic Dearing strain reovirus or an oncolytic ONYC-015 virus, wherein the volume of the virus composition is between about 10% and about 100% of the tumor volume (and at least 50% of the tumor volume), wherein the virus is delivered to multiple sites in the tumor, wherein the virus is administered by injection into one site per about 0.25 cc of the tumor, and wherein the method further comprises at least one additional administration of a Dearing strain virus by systemic administration, or topical/transdermal patch/spray on the skin when the tumor is a superficial tumor with a reasonable expectation of success.

The motivation to make such a modification is supplied by Heise who specifically teaches that increasing the distribution of an oncolytic virus solution in a tumor, by means such as using multiple injections or increasing the volume of the oncolytic viral solution that is administered can increase the efficacy of the treatment.

It would further have been prima facie obvious to perform routine optimization to determine the most effective number of administrations or the exact volume of viral composition administered. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the injecting an oncolytic viral composition to multiple sites in a tumor the same day wherein the number of sites injected is at least 3 sites or at least 5 sites inside the tumor results in an unexpected result in view of the closest prior art. The closest prior art being (1) Heise, which teaches increasing the distribution of an oncolytic virus composition in a tumor (by using multiple injections or adjusting the volume of the composition that is administered) increases the efficacy of the treatment, and (2) Lee, which teaches treating tumors by administering an oncolytic virus in multiple doses wherein the doses can be administered concurrently (i.e., on the same day).

Applicant's arguments, see pages 5-14 of the reply filed 9/23/04, with respect to the rejection(s)of claim(s) under USC 112, 102 and 103 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the teachings of Lee and Heise, as indicated above.

With respect to Applicants arguments as they pertain to the instant rejection, Applicants argue that Lee does not specifically teach or suggest multiple injections of the viral composition intro the tumor on the same day.

In response, it is respectfully pointed out that Lee specifically teaches, "The reovirus can be administered in a single dose or in multiple doses (i.e., more than one dose). The multiple doses can be administered concurrently or consecutively (e.g., over a period of days or weeks)."

(See page 9, lines 17-20). Therefore, Lee does specifically teach and suggest multiple injections of the viral composition intro the tumor on the same day.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.
Art unit 1635

DAVE T. NGUYEN
PRIMARY EXAMINER